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General

Brivaracetam to Treat Partial Onset Seizures in Adults

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Purpose of Review

Seizures are a hyperexcitable, and hypersynchronous imbalance between excitatory and inhibitory factors (E/I imbalance) in neurotransmission, and epilepsy is the recurrent manifestation of seizures within a reasonable time frame and without being attributable to a reversible cause. Brivaracetam is a derivative of the antiepileptic agent, levetiracetam, that is used as adjuvant therapy for focal onset seizures. It was approved by the FDA in 2016 and has shown promising results with minimal adverse effect reactions in clinical trials.

Recent Findings

Brivaracetam has been used in multiple clinical trials at various dosages in adults that have partial-onset seizures refractory to conventional treatment. A meta-analysis in 2016 showed that brivaracetam as adjunctive therapy was statically significant in its reduction of adults with drug-refractory seizure frequency.¹ The most commonly reported adverse effects that patients who were taking brivaracetam experienced were somnolence, headache, and dizziness. Further studies are necessary to conclude long term efficacy and safety profile of brivaracetam.

Conclusion

The treatment of epilepsy with pharmacologic agents is a difficult task due to balancing the efficacy of the drug with the side effect profile that will allow for the best quality of life for the patient. There are approximately 30 antiepileptic agents for clinicians to choose from. Brivaracetam is a novel antiepileptic agent that was approved for use by the FDA in 2016 and is showing promising results as monotherapy and adjunctive therapy in individuals with drug-refractory focal seizures while minimizing adverse drug reactions.

INTRODUCTION

A seizure is classically defined as an uncontrolled burst or disturbance of synchronous electrical activity between neurons.¹ Loss of consciousness, sensation changes, involuntary twitching or stiffening, and other physiological ab-

normalities can manifest with this disturbance. Determining the nature or predisposing event of the activity is a vital factor for clinicians to effectively localize and treat the problem. Variability does exist among seizures, and the repetitive spontaneous episodes of these electrical changes are termed epilepsy.² In contrast, a variety of nonepilep-

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ILAE 2017 Classification of Seizure Types Expanded Version ¹

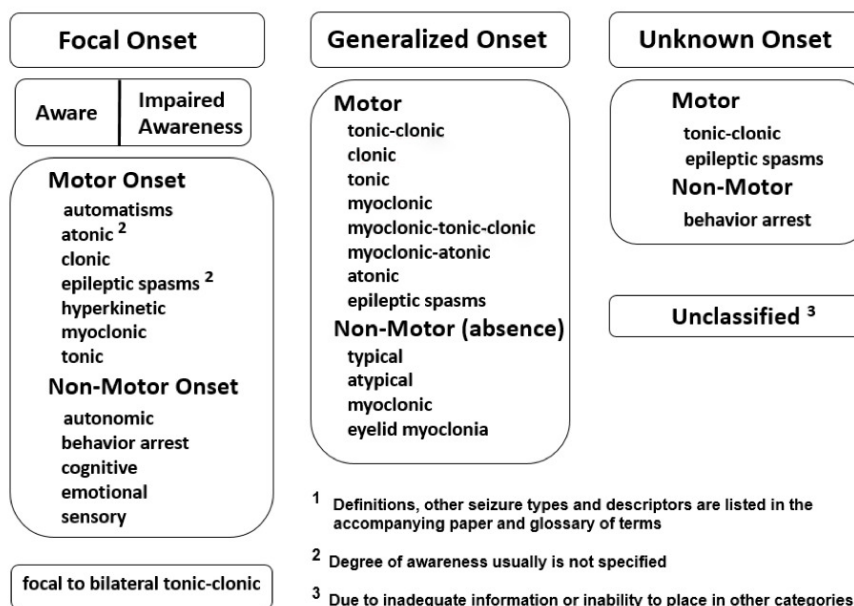


Figure 1. ILAE 2017 Classification of Seizure Types

tic seizure causes include (but are not limited to) emotional stress, movement disorders, and psychogenic seizures. These nonepileptic seizures will appear symptomatically similar to epileptic seizures, but the difference lies in the fact that there is no unusual electrical activity within the neurons.³ Psychogenic nonepileptic seizures (PNES) can be extremely difficult to identify even for an experienced clinician or researcher, due to the wide variety of underlying causes for the episodes and similar presentation to an epileptic seizure. Observational examination, electroencephalography (EEG) monitoring during seizure episodes, sleep activity imaging, and stressor/trigger determinations can all aid with the process of distinguishing a PNES episode from epileptic seizures.

Epilepsy, as previously mentioned, is characterized as the chronic disorder of hypersynchronous neuronal electrical disturbances that recurrently occur.⁴ This differs from an isolated seizure in the fact that the isolated seizure is a single episode with no consistent pattern or recurrent episode. Epilepsy also differentiates itself from seizures of other causes that are resolved with treatment of the secondary cause such as metabolic abnormalities, electrolyte disturbances, or head trauma. Discrimination of epilepsy from the aforementioned types is important for the classification of the seizure. The International League Against Epilepsy (ILAE) created a classification system to define consistent parameters and characterize the separate epileptic seizure types. Using the new 2017 ILAE classification, an accurate diagnosis can be made at different levels (Figure 1).

The first level includes the seizure type. In order for this level to be fulfilled, the clinician or researcher must indicate and conclude that the seizure is indeed epileptic in contrast to a differential paroxysmal episode.⁵ Epileptic

seizure type can then be divided into: generalized onset seizures, focal onset seizures, and unknown onset seizures. The generalized seizure is described as originating in bilaterally distributed neuronal networks, in contrast to the focal seizures that begin in neuronal networks limited to one part of the cerebral hemisphere. The unknown onset type of epileptic seizure demarcates the case where the onset is unknown or there is not adequate information to place the seizure into the other categories.⁵

These 3 epileptic seizure types (generalized, focal, and unknown) can be further divided in order to make a more specific diagnosis while removing ambiguity among the different presentations. The generalized seizures are next classified as either motor or non-motor/absence. The generalized motor seizure is further broken down into variants such as tonic, clonic, tonic-clonic variant, atonic, and myoclonic. Tonic motor seizures involve episodes of bilateral hypertonia of the limbs that may range from seconds to a minute. The muscle stiffening with this seizure is often accompanied by intellectual impairment during this presentation. The clonic motor seizure involves the bilateral presentation of sustained rhythmic jerking with the loss of consciousness. The myoclonic motor seizure presents as a series of brief, irregular jerks that are milliseconds in duration. The final type of generalized motor seizure is the atonic seizure. The atonic motor seizure involves the sudden loss of muscle tone lasting less than 2 seconds in duration and often with intellectual impairment.

The non-motor (absence) generalized seizure which was formerly referred to as petit mal are broken down further to include: typical, atypical, myoclonic, and absence with eyelid myoclonia. The difference between absence typical and absence atypical is that a typical seizure has an abrupt onset with movements around 3Hz, while atypical has a less

abrupt onset with the movement <2.5 Hz. The myoclonic absence seizure is described as rhythmic myoclonic jerks of the shoulders and arms with tonic abduction that result in the lifting of the arms during the seizure. This type of absence seizure tends to range from 10-60 seconds and also involves changes in awareness ranging from total loss to complete awareness being maintained during the episode. Lastly, the absence seizure with eyelid myoclonia is described as quick 4-6 Hz myoclonic jerks of eyelids with an upward deviation of the eyes and extension of the head lasting less than 6 seconds. Overall, these distinct classifications provide clinicians with a valuable tool for making an accurate diagnosis from the different presentations.

EPIDEMIOLOGY

Seizures are a very common neurological problem. An estimated 10 percent of the population will have at least one seizure over the course of a lifetime. Seizures are either provoked or unprovoked. A “provoked” seizure implies that a secondary medical condition is causing one’s seizure. These seizures generally resolve after treating the neurologic insult. An “unprovoked” seizure is associated with epilepsy and implies that no reversible factor is causing a patient’s seizure. Approximately 1 to 2 percent of all ED visits are due to seizures, with 25 percent of these being a patient’s first seizure.⁶ Regarding epilepsy, 40-52 percent of patients with a single unprovoked seizure will have another seizure within their lifetime, with the highest risk of recurrence within the next 2 years.^{6,7} The risk of having another seizure increases to 73 percent if a patient has had two unprovoked seizures.⁸ The incidence of epilepsy is 50 cases per year per 100,000 population. Nearly 1 percent of the population has epilepsy, and refractory epilepsy (i.e., uncontrolled seizures despite following established treatment guidelines) occurs in 33 percent of these patients. Most patients (75%) develop epilepsy during childhood, underlying an increased susceptibility of the immature brain to the development of seizures.⁹

PATHOPHYSIOLOGY OF SEIZURES AND EPILEPSY

Provoked seizures can arise from a variety of causes and do not constitute epilepsy. Many identifiable causes of seizures exist, including vascular disturbances, infection, trauma, autoimmune etiologies, metabolic alterations, neoplastic change, drug intoxication or withdrawal, and seizures of psychiatric origin. However, certain chronic medical conditions may involve unprovoked seizures that meet the clinical definition of epilepsy. In this circumstance, the definition of epilepsy is blurred, and management should involve treating both seizures and other manifestations of the causative disease.⁸ Under normal circumstances, stable neuronal membranes maintain a balance between the excitation and inhibition of neuronal signals. When the stability of the membrane is disrupted due to any of the above factors, seizures are provoked.¹⁰ For

example, chronic alcohol consumption induces insensitivity to GABA such that more ethanol is needed to maintain a normal inhibitory tone.¹¹ When patients abruptly stop drinking, the excitation/inhibition ratio is increased, causing a seizure.

Epileptic seizures are unprovoked. While the pathophysiology is complex and incompletely understood, epileptic seizures are still thought to be due to a distortion of the normal excitation and inhibitory balance in the brain. This imbalance can result from changes at many levels of neuronal function, including gene mutations, aberrant subcellular signaling, or dysfunctional neuronal networks. Some examples of epilepsy syndromes resulting from genetic mutations include benign familial neonatal epilepsy, West syndrome, Dravet syndrome, Lennox-Gastaut syndrome, Landau-Kleffner syndrome, and juvenile myoclonic epilepsy. Younger patients are particularly susceptible to the development of epilepsy due to many physiologic mechanisms. Excitatory synaptic function develops before inhibitory synaptic function, predisposing to unprovoked seizures. Additionally, there is evidence that GABA causes excitation rather than inhibition in immature brains, further elucidating why epilepsy tends to develop in young people.⁹

DIAGNOSIS

Diagnosing seizures and epilepsy relies heavily on history taking and neurologic examination. A general physical examination also aids in diagnosis. For example, skin abnormalities may point to a neurocutaneous disorder in which epilepsy is common. The primary goal in evaluating a patient’s first seizure is determining whether the seizure is due to a treatable systemic cause or intrinsic brain dysfunction. Establishing the cause of the presenting seizure guides the prognosis, therapy, and likelihood of having additional seizures.⁹ The clinical criteria of epilepsy is met when a patient has any of the following: at least two unprovoked seizures occurring more than 24 hours apart; one unprovoked seizure and a probability of future seizures similar to the general recurrence risk after two unprovoked seizures (60%) occurring over the next 10 years; or the diagnosis of an epilepsy syndrome.⁸

Any patient who has a seizure should undergo electroencephalography (EEG). It has been found that 12-50 percent of adults and 18-56 percent of children with a single seizure had epileptiform abnormalities on EEG. EEG can also detect the type of seizure. Absence seizures, atonic or myoclonic seizures, focal seizures with impaired awareness, and generalized tonic-clonic seizures are associated with EEG abnormalities in 92%, 85%, 59%, and 44% of cases, respectively. EEG abnormalities also give information regarding seizure recurrence. In adults, the presence of epileptiform discharges for seizure recurrence has a sensitivity of 17.3 percent and a specificity of 94.7 percent, corresponding to a 77 percent post-test probability of seizure recurrence in patients with epileptiform discharges and a 47 percent post-test probability in those without. For children, EEG demonstrates a sensitivity of 57.8 percent and a specificity of 69.6 percent for seizure recurrence. This corresponds to a post-

test probability of 66 percent when EEG findings are positive for epileptic discharge, compared to 38 percent when absent. EEG testing relative to the timing of the seizure may influence the ability of the EEG to detect recurrence risk. While clinical data on this topic is limited, one hypothesis states that the brain is most excitable immediately following a seizure, with decremental excitability over time. Therefore, EEG recordings should be done as soon as possible to detect the presence of epileptiform change.⁷

If epileptiform changes are not detected on the initial EEG, subsequent EEGs should be performed. While this seems paradoxical due to the temporal relationship between EEG recordings and the timing of seizure, multiple recordings were found to increase the yield of observing epileptiform discharges in patients whose initial recording was negative. It was found that only half of the patients with suspected epilepsy will have epileptiform changes on initial EEG screening. The yield increased to 84 percent after three recordings and 92 percent after four recordings. Serial EEG studies may be performed in a variety of ways, including sleep deprivation EEGs, video recording EEGs, and ambulatory EEGs. All have been shown to increase the diagnostic yield of epilepsy, and it seems that the use of one over the other is due to clinician judgement in a given scenario.^{7,12}

Neuroimaging should also be performed in patients with a first seizure to check for any gross abnormalities. Magnetic resonance imaging is preferred over computer tomography in a non-emergent setting, as it is more sensitive. Less common tests include functional magnetic resonance imaging (fMRI), positron emission tomography, single-photon emission computed tomography, magnetoencephalography, and magnetic source imaging. These tests are used primarily in the presurgical evaluation of patients with medically refractory epilepsy. Routine blood work is also routinely ordered during work up to detect any electrolyte abnormalities, changes in blood cell count, etc. A lumbar puncture may also be helpful if the seizure is suspected to be due to an infectious cause and space-occupying brain lesions have been ruled out.^{13–15}

PRESENTATION AND RISK FACTORS

The presentation of epilepsy is highly variable. Oftentimes, patients will have only one seizure with EEG findings consistent with a high risk of recurrence. The second seizure may arise days or even years later. Patients with epilepsy can have any type of seizure, ranging from focal to generalized and convulsive to non-convulsive.^{8,10} Some patients may have triggers for their epileptic events including visual auras, bowel problems, stress, sleep disturbances, photosensitivity, and hormonal imbalances.^{16,17} The duration of most seizures is generally less than 5 minutes. A seizure lasting more than 5 minutes is called status epilepticus (SE). SE can lead to permanent brain damage and is thus a medical emergency. Fortunately, most first time seizures are brief in duration.¹⁸ Postictal periods are common amongst seizure patients. The mean duration for returning to consciousness does not differ amongst children

and adults. However, associated signs may differ between the two groups. For example, postictal paralysis (“Todd paralysis”) is more likely to occur in the elderly. Other postictal signs exist and may point to specific regions of the brain.¹⁹ Epilepsy is not always a lifelong condition. For example, epilepsy can resolve if a patient receives surgical intervention or if a patient outgrows an age-dependent epilepsy syndrome. If a patient has had no seizures for at least 10 years without the use of anticonvulsants for at least the last 5 years, a patient is no longer classified as having a diagnosis of epilepsy.⁸ Certain populations have a higher risk of developing epilepsy. These include people with developmental delay, intellectual disability, a positive family history of febrile seizures and epilepsy, cerebrovascular insults, cerebral infection, and brain trauma.^{20–23}

PARTIAL ONSET SEIZURES IN ADULTS

The neurophysiological identification factors for partial (focal) seizures are clear under electroencephalogram (EEG) and presurgical depth electrode recordings. Replicated patterns for each event such as the initiation, progression/propagation, and termination of seizures have been recorded, but the exact network determinants that explain the interictal spikes are not fully understood. Examination of commonalities among EEG patterns can be useful in forming a diagnosis. The initiation stage of a focal seizure on an EEG appears a flattened signal with low amplitude and rapid rhythms.²⁴ The neurons and glia involved in a focal seizure experience changes in structure and function that may result from epileptogenic episodes triggered by primary insult damage such as trauma or inflammation.²⁵ After the hypersynchronous initiation signal is generated, further recorded signals indicate a transition into tonic discharge.²⁶ The expected cause of the transition may include shifts in extracellular potassium concentration with the increased interneuronal activity.²⁷ The ramification of this extracellular potassium shift decreases the chloride ions’ electrochemical gradient, weakening the inhibitory network at the seizure initiation stage.²⁸ In the termination process of a focal seizure, signals indicate another transition from the tonic firing activity of the signal propagation stage into rhythmic bursting. The resynchronization of intracranial signals is expected to be involved in the large amplitude, interburst activity increases just prior to termination.^{25,29,30} These focal seizures are understood to be self-limiting and result in termination after a roughly 2-6 minute duration.³¹

After forming the diagnosis based on electrical disturbances, creating a proper treatment plan tailored for the individual is the next step in treating this disorder to improve the patient’s quality of life. While the optimal antiepileptic treatment would eliminate seizure activity entirely with no adverse effects, current antiepileptic therapy has not proven to be completely effective in doing so. Given that the causes and severity of epilepsy can vary widely, the treatment options vary by patient. Results of efficacy for certain treatments differ based on a number of factors such as types of seizures, genetics, and severity of neurological

alterations that occur during the disorder. While there is still much to discover to find the best courses of action for treatment, studies have proven that more favorable prognoses are achieved in early diagnosed patients.³²

The standard approved treatment, for generalized tonic-clonic, atypical absence, myoclonic, and atonic seizures, is the first line agents such as valproic acid, lamotrigine, and topiramate. While these same drugs may be used in alternative treatments for focal seizures, the primary approved treatment option for partial seizures includes drugs such as carbamazepine, phenytoin, and oxcarbazepine.³³ For alternative treatment options for partial seizures, adjunctive therapy utilizing valproic acid, topiramate, and levetiracetam have proven to be effective in some cases. While these are the typical standards of treatment, other options outside of pharmacological therapy do exist as well.

Mechanical vagus nerve stimulation (VNS) is a mechanical treatment option being used today to reduce seizures. Early animal studies supported the effectiveness of the treatment option, and it was later approved in Europe in 1994. The United States and Canada followed suit and approved the use of VNS in 1997.³⁴ The treatment involves placing helical electrodes onto the patient's left vagus nerve followed by sporadic stimulation from a neurocybernetic prosthetic device implanted subcutaneously in the upper chest.³⁵ Clinical trials have been shown to decrease the incidence of complex partial seizures significantly, with results in some cases indicating as much as 20-40% of the patients receiving a result of a greater than 50% decrease in seizure frequency.^{36,37} Overall, this mechanical treatment does appear to be a viable option for non-pharmacological therapy in some cases.

BRIVARACETAM DRUG INFORMATION

Brivaracetam is an antiepileptic propyl analog of levetiracetam that was the Food and Drug Administration (FDA) approved in 2016.³⁸ It is currently listed as a Schedule V substance, and indications of the FDA label supports the treatment of partial-onset seizures in adult patients (16 years of age and older). The current recommendation is oral administration, but injection may be used when oral administration is impossible. According to the FDA label, brivaracetam displays linear and time-independent pharmacokinetics when used in the approved dosages. While the exact mechanism of action is not yet understood, the effects are likely a result of the drug's highly selective affinity for synaptic vesicle protein 2A (SV2A) in the brain. Mouse studies with SV2A deficient variants indicate a lower threshold for developing seizures.³⁹ In 2018, a study reviewed 6 Brivaracetam trials from 1946-2018 with a total of 2411 participants. Results of the study indicated that participants using the drug as an add-on therapy for epilepsy were significantly more likely to experience a 50% or greater reduction in seizure frequency compared to the placebo.⁴⁰ With a greater understanding of this drug coming to light, the efficacy, tolerability, and mechanism of action will aid researchers and clinicians in determining its viability as a treatment option for drug-resistant epilepsy.

MECHANISM OF ACTION/PHARMACODYNAMICS

Brivaracetam is a 4-n-propyl derivative of levetiracetam that is used as adjuvant therapy for focal onset seizures. The exact mechanism of action is unclear. However, its anticonvulsant properties are believed to be due to its high affinity for the synaptic vesicle protein 2A (SV2A) found in the brain.^{38,41-43}

SV2A is a transmembrane glycoprotein that has many functions in signal transduction. While its role in neuronal physiology is not completely understood, evidence suggests that SV2A is involved in virtually every step of neurotransmitter release, making it a promising target in treating seizures. SV2A regulates neurotransmission through its interaction with synaptic vesicles. It primes vesicles for the release of neurotransmitters once neuronal signals are transmitted. Additionally, SV2A directly regulates neurotransmitter release and uptake. It has been demonstrated that null SV2A animals have an increased risk of seizure development.^{38,41} Therefore, it's possible brivaracetam may decrease the seizure threshold by upregulating SV2A's activity in patients with decreased SV2A activity.

The binding of brivaracetam may also be beneficial in treating seizures by decreasing SV2A's activity. It's hypothesized that SV2A binding by brivaracetam results in decreased exocytosis of neurotransmitters and neural response to rapid stimuli by inhibiting vesicular transport. Brivaracetam appears to enter synaptic vesicles during recycling and endocytosis in hyperexcitable synapses to elicit this effect. Another hypothesis states that brivaracetam induces a conformational change in overactive SV2A, stabilizing the protein.⁴¹

While brivaracetam is a structural analog of levetiracetam, its interaction with cell surface receptors is minimal. Levetiracetam binds and inhibits AMPA receptors and high-voltage-calcium channels.^{41,42} This effect is not observed in brivaracetam and only exerts a minor inhibitory effect on NMDA receptors at very high concentrations.⁴¹ Earlier studies found that brivaracetam may inhibit voltage-gated sodium channels. However, this finding was later debunked — both brivaracetam and levetiracetam bind SV2A.^{41,42}

Side effects of brivaracetam include fatigue, dizziness, and somnolence, although the drug is generally well-tolerated.⁴² Limited data are known about the effects of brivaracetam in pregnant women, although animal models demonstrated that toxicity is possible. The use of brivaracetam in pediatric patients is not well established, but juvenile animals were found to potentially have adverse effects.³⁸

PHARMACOKINETICS

Brivaracetam is absorbed well by the body when given orally, with a median time to maximal concentration (t_{max}) between 1 and 2 hours.⁴³ The bioavailability of brivaracetam is nearly 100 percent. Brivaracetam is absorbed passively in the gastrointestinal tract and has a linear and dose-related absorption profile.⁴² Diets high in fats were found to alter brivaracetam absorption, increasing the t_{max}

to 3 hours, and decreasing the maximal concentration (C_{max}). However, high-fat diets were not found to change the area under the plasma concentration curve. Plasma protein binding is minimal (less than 20%).^{41,42} For this reason, one can speculate that extensive tubular reabsorption is present in healthy subjects.⁴³ Brivaracetam plasma levels are highly correlated with levels in saliva.^{41,42} Therefore, it may be useful to monitor brivaracetam saliva levels in patients where blood monitoring is unreliable or contraindicated.⁴² The volume of distribution of brivaracetam is nearly the same as that of water. Brivaracetam is metabolized by hydrolysis by an amidase followed liver CYP450 metabolism, specifically CYP2C9 and CYP2C19. Its metabolites do not appear to be active and are primarily cleared by the kidney. Therefore, patients with renal impairment do not likely require dose adjustments. However, liver dysfunction reduces the metabolism of brivaracetam, and plasma levels increase by up to 60 percent in these patients.^{41,42} Brivaracetam was found to not significantly increase or decrease hepatic CYP450 activity. However, since brivaracetam metabolism is altered by CYP450 induction or inhibition, it should be used carefully in patients taking other anticonvulsants such as phenytoin, valproic acid, and carbamazepine. Brivaracetam's interaction with alcohol is not clearly defined. However, clinicians should be cautious in prescribing brivaracetam to patients with a history of alcohol abuse, as certain reports found that brivaracetam increases alcohol-induced motor, attention, and memory dysfunction.⁴¹

CLINICAL TRIALS

Published in 2010, French et al. performed a phase IIb, double-blind, randomized, parallel-group, placebo-controlled, dose-ranging study (randomized (1:1:1:1) to placebo, BRV 5 mg/day (BRV5), BRV 20 mg/day (BRV20), or BRV 50 mg/day (BRV50)) administered BID during a 7 week treatment period.⁴⁴ Two hundred eight patients ranging in age from 16–65 years old with epilepsy experiencing ≥ 4 POS (refractory partial-onset seizures) during a 4-week baseline despite 1–2 concomitant antiepileptic drugs.⁴⁴

Paesschen et al. performed a phase IIb, double-blind, randomized, placebo-controlled, parallel-group, dose-ranging study (randomized to BRV 50 mg/day, 150 mg/day, or placebo).⁴⁵ A total of 157 patients ranging in age from 16–65 years old with 4 or more POS during a 4-week baseline despite treatment with 1–2 concomitant antiepileptic drugs were enrolled with intent-to-treat with 148 completing the study.⁴⁵ A 7-week maintenance period was observed with a total treatment period of 10 weeks.⁴⁵

Conducted between September 2007 and February 2009, Rylvlin et al. performed a phase III, double-blind, randomized, placebo-controlled, fixed-dose-ranging study (randomized to BRV 20, 50, 100 mg/day, or placebo).⁴⁶ A total of 398 patients ranging from 16–70 years old with focal epilepsy or epileptic syndrome with 2 or more focal seizures/month for 3 months prior to screening and eight or more focal seizures during an 8-week prospective baseline period who were also receiving 1 or 2 concomitant

AEDs.⁴⁶ Of those 398, 367 patients completed the study.⁴⁶ The treatment period was 12 weeks.⁴⁶

Conducted between September 2007 and January 2009, Biton et al. performed a phase III, prospective, multicenter, randomized, double-blind, placebo-controlled, parallel-group, fixed-dose trial with patients receiving either twice-daily placebo (PBO) or BRV (5, 20, or 50 mg/day).⁴⁷ A total of 396 patients ranging from 16–70 years old with well-characterized partial epilepsy not fully controlled despite treatment with one or two antiepileptic drugs were enrolled during an 8-week baseline period with a 12-week treatment period.⁴⁷

Conducted between October 2007 and December 2008, Kwan et al. performed a phase III, prospective, multicenter, randomized, double-blind, placebo-controlled, parallel-group, a flexible-dose trial where BRV was administered twice daily in equal doses.⁴⁸ During the dose-finding period, BRV was initiated at 20 mg/day and uptitrated in a stepwise manner to 50, 100, or 150 mg/day, at 2-week intervals based on the investigator's assessment of efficacy and tolerability (with patients on placebo receiving matching placebo tablets).⁴⁸ There was an 8-week dose-finding followed by an 8-week maintenance, which was then followed by down-titration or entry into long-term follow-up.⁴⁸ Patients were randomized 3:1 in random permuted blocks to BRV or PBO at the end of the baseline period.⁴⁸ Randomization was stratified by epilepsy type (focal or generalized), concomitant levetiracetam (LEV) use (yes or no), and geographic region.⁴⁸ There were a total of 480 randomized patients (BRV 359, PBO 121) and of these, 431 had focal epilepsy and 49 had generalized epilepsy.⁴⁸

Patient enrollment occurred from December 2010 to December 2013, Klein et al. performed a phase III, randomized, double-blind, PBO-controlled, multicenter, parallel-group study where patients were treated with placebo, BRV 100 mg/day, or BRV 200 mg/day.⁴⁹ A total of 768 patients were enrolled with 696 completing the study, patients ranged in age from 16–80 years, with well-characterized focal epilepsy or epileptic syndrome, uncontrolled with one or two concomitant AEDs at stable dosage for at least 1 month before visit 1 (3 months for phenobarbital, phenytoin, and primidone).⁴⁹ The study consisted of an 8-week prospective baseline period, a 12-week treatment period, and a 4-week down-titration period followed by a 2-week drug-free period, or entry into a long-term follow-up study.⁴⁹

EFFICACY

French et al. observed median percent reductions from baseline in POS frequency/week were 21.7% (placebo), 29.9% (BRV5; $p = 0.086$), 42.6% (BRV20; $p = 0.014$), and 53.1% (BRV50; $p < 0.001$), the study seemed to demonstrate an increase in effectiveness as the dosage was increased from 5mg/day to 50mg/day.⁴⁴ French et al. observed a statistically significant average percent reduction in weekly seizure occurrences of 41.8% across BRV doses of 5mg, 20mg, and 50mg as compared to a percent reduction of 21.7% observed in placebo.⁴⁴ Of note there seemed to be a

linear increase in effectiveness of BRV as dosages were increased from 5mg/day to 50mg/day.

Paesschen et al. noted that within a 7-week maintenance, the median partial-onset seizure frequency/week was 1.00 (0.71–2.38), 1.96 (1.14–3.07), and 1.86 (0.94–4.69) in the BRV 50 mg/day, BRV 150 mg/day, and placebo groups, respectively with a percent reduction in baseline-adjusted partial-onset seizure frequency/week over placebo during the maintenance period being 14.7% (–2.7, 29.2; $p = 0.093$) in the BRV 50 mg/day group and 13.6% (–4.1, 28.3; $p = 0.124$) in the BRV 150 mg/day group.⁴⁵ However, during the 10 weeks the median partial-onset seizure frequency/week was 1.10 (0.70–2.00), 2.05 (1.01–3.32), and 1.95 (1.05–5.12) in the BRV 50 mg/day, BRV 150 mg/day, and placebo groups, respectively with a percent reduction over placebo in the partial-onset seizure frequency/week were observed in the BRV 50 mg/day (17.7%; 95% CI 2.3, 30.7; $p = 0.026$) and BRV 150 mg/day (16.3%; 95% CI 0.6, 29.5; $p = 0.043$) groups.⁴⁵ In summary, Paesschen et al. noted a nonsignificant average percent reduction in partial-onset seizure frequency per week of 14.5% in 50 mg/d and 150 mg/d of BRV during week 7 of treatment.⁴⁵ Patients achieved a significant average percent reduction in partial-onset seizure frequency per week of 17% in 50 mg/d and 150 mg/d of BRV by week 10 of treatment.⁴⁵ The emergence of statistically significant reductions in POS over placebo may hint at a possible maintenance period needed for stable/effective levels of BRV to be achieved within patients.

Ryvlin et al. noted median percent reductions from baseline were 30.0% for BRV 20 mg/day, 26.8% for BRV 50 mg/day, and 32.5% for BRV 100 mg/day compared with 17.0% for placebo ($p = 0.019$, $p = 0.092$, and $p = 0.004$, respectively), of note percent reduction over placebo in focal seizure frequency only achieved statistical significance at the 12-week treatment period.⁴⁶ In summary, Ryvlin et al. noted a significant average 29.77% percent reduction in seizure frequency per week as compared to a 17% reduction observed in placebo patients.⁴⁶ Of note significance was only achieved after a 12-week treatment period.⁴⁶ The emergence of statistically significant reductions in POS over placebo may hint at a possible maintenance period needed for stable/effective levels of BRV to be achieved within patients.

Biton et al. noted that after the 12-week treatment period, the median percent reduction from baseline in partial-onset seizure frequency/week was 17.8% for placebo compared with 20.0% for BRV 5 mg/day, 22.5% for BRV 20 mg/day, and 30.5% for BRV 50 mg/day.⁴⁷ The reduction was statistically significant in the 50 mg/day BRV group ($p = 0.003$) while statistical significance was not found for BRV 5mg/day and BRV 20 mg/day.⁴⁷ This may note the importance of higher dosing (until a limit is reached).

Klein et al. found that “percent reduction over placebo in 28-day adjusted seizure frequency (95% confidence interval [CI]) was 22.8% for BRV 100 mg/day (13.3–31.2%; $p < 0.001$) and 23.2% for BRV 200 mg/day (13.8–31.6%; $p < 0.001$)”.⁴⁹ Of note, “response to BRV 100 mg/day was seen across all regions, however, for BRV 200 mg/day, there appeared to be a higher response in North America, Latin America,

Asia-Pacific/Other countries, and non-EU European countries than in EU countries. For $\geq 50\%$ responder rate, the placebo response was highest in non-EU European countries and lowest in Asia-Pacific/Other countries.”⁴⁹ These results indicate a possible genetic component in response to higher doses of BRV.

Ben-Menachem et al. noted a reduction in POS of an efficacy population of $n=1160$ over placebo (95% confidence interval) in baseline-adjusted POS frequency/28 days was 19.5% (8.0%–29.6%) for 50 mg/d ($p = 0.0015$), 24.4% (16.8%–31.2%) for 100 mg/d ($p < 0.00001$), and 24.0% (15.3%–31.8%) for 200 mg/d ($p < 0.00001$).⁵⁰ Ben-Menachem et al. noted statistically significant decreases in seizure occurrences at doses of 50 mg/d, 100 mg/d, and 200 mg/d.⁵⁰ Of note, there was a decrease in the percent reduction of seizure occurrences as the doses increased from 100 mg/d (seizure reduction of 24.4%) to 200 mg/d (seizure reduction of 24%).⁵⁰ There may be a threshold to positive effects of BRV due to the decrease from 100mg/day to 200 mg/day.

Lattanzi et al. performed a meta-analysis of 6 trials involving 2,399 participants according to the intent-to-treat, 1,715 for BRV, and 684 for placebo groups.⁵¹ The pooled risk ratio for 50% responders and seizure freedom were 1.79 (1.51–2.12) and 4.74 (2.00–11.25), respectively.⁵¹ No statistically significant difference in the 50% responder rate was found when comparing BRV with placebo in patients with concomitant assumption of LEV.⁵¹

Klein et al. performed a review of phase 1-3 data of Brivaracetam use in therapy for epilepsy including animal data as well.⁵² Phase 1 evaluated single oral doses ranging from 5-800 mg with repeated oral doses of up to 600 mg were well tolerated and demonstrated favorable pharmacokinetic outcomes.⁵² Phase 2 showed safety and tolerability in the dose range of 5-150 mg/day with proof of efficacy in the treatment of refractory partial onset seizures.⁵² 4 Phase 3 trials have shown efficacy in the range of 100-200 mg/day with safety and tolerability being present in the dose range of 5-200 mg.⁵²

Benbadis et al. conducted a post-hoc analysis of 3 phase III randomized, double-blind trials evaluating the efficacy of adjunctive BRV with concomitant lamotrigine and topiramate use where an efficacy population comprised 220 patients in the lamotrigine subgroup and 122 patients in the topiramate subgroup with the safety population comprising 245 patients in the lamotrigine subgroup and 125 patients in the topiramate subgroup.⁵³ BRV administered with concomitant lamotrigine or topiramate was found to be effective in reducing seizure frequency and was generally well tolerated for BRV doses ranging from 50-200mg/day.⁵³ In summary, Benbadis et al. showed that BRV with concurrent use of lamotrigine or topiramate demonstrated efficacy in reducing seizure frequencies as well as showing good tolerance at doses ranging from 50-200 mg/d.⁵³

SIDE-EFFECTS AND ADVERSE EVENTS

Moseley et al. pooled data from five randomized, double-blind, placebo-controlled efficacy studies (NCT00175929,

NCT00175825, NCT00490035, NCT00464269, and NCT01261325) with an n= 1402, in which adults with refractory epilepsy, and receiving stable doses of 1–2 commonly prescribed epileptic drugs, initiated adjunctive treatment with BRV (or placebo) for up to 12 weeks.⁵⁴ Concentrations of carbamazepine, carbamazepine epoxide, clobazam, clonazepam, lacosamide, lamotrigine, levetiracetam, oxcarbazepine (MHD), phenobarbital, phenytoin, pregabalin, topiramate, valproic acid, and zonisamide, were measured during baseline and during BRV or placebo evaluation periods revealing only an increase of up to 2-fold of carbamazepine oxide alone from baseline due to inhibition of epoxide hydrolase by BRV.⁵⁴

Ben-Menachem et al. noted specific treatment-emergent adverse effects of brivaracetam vs placebo that included somnolence (15.2% vs 8.5%), dizziness (11.2% vs 7.2%), headache (9.6% vs 10.2%), and fatigue (8.7% vs 3.7%).⁵⁰

Lattanzi et al. identified BRV-specific treatment-emergent adverse to be irritability (2.99 [1.28–6.97]), fatigue (2.19 [1.44–3.33]), somnolence (1.97 [1.45–2.68]), and dizziness (1.66 [1.19–2.31]).⁵¹

Biton et al. observed that over 70% of patients on BRV of any dose experienced at least one treatment-emergent adverse effect.⁴⁷ Significant TEAEs included somnolence and dizziness (all three BRV doses); fatigue (BRV 20 and 50 mg/day); influenza (BRV 5 and 20 mg/day); nausea and urinary tract infection (BRV 20 mg/day); and diarrhea, insomnia, vomiting and nasopharyngitis (BRV 50 mg/day).⁴⁷ Of note, no clear dose-response was noted to increase the incidence of specific TEAEs in the 3 BRV doses.⁴⁷

Kwan et al. noted during the treatment period, the most frequently reported adverse effects (>8% in the BRV group) were headache (BRV 14.2%, PBO 19.8%), somnolence (BRV 11.1%, PBO 4.1%), and dizziness (BRV 8.6%, PBO 5.8%).⁴⁸ Irritability was reported in 7 (1.9%) of 359 patients in the BRV group and 0 of 121 patients in the placebo group.⁴⁸ Aggression was reported in 5 (1.4%) of 359 patients in the BRV group versus 1 (0.8%) of 121 in the placebo group. Serious side effects observed were convulsions (10 occurrences; BRV 9/359, 2.8%; PBO 1/121, 0.8%) and status epilepticus (three occurrences, all in a single patient randomized to BRV who had discontinued BRV at the time of serious adverse events).⁴⁸ One death occurred during the maintenance period (patient receiving BRV 50 mg/day) (however the death was attributed to drowning while the patient was swimming and was considered likely to be caused by a seizure while in the water).⁴⁸

Benbadis et al. found that the treatment-emergent adverse effects most frequently reported by all patients taking BRV were somnolence (21.3% overall), dizziness (11.5% overall), and fatigue (9.8% overall), which were the same for both the lamotrigine and topiramate subgroups.⁵³ Variations in the incidence of each side effect for different doses

of brivaracetam were attributed to the small sample sizes used.⁵³

Klein et al. found that treatment-emergent adverse effects were reported in 155 (59.4%) of 261 patients in the PBO group, 173 (68.4%) of 253 patients in the BRV 100 mg/day group, and 167 (66.8%) of 250 patients in the 200 mg/day group.⁴⁹ The most frequently reported adverse effects were somnolence (18.1% in BRV overall), dizziness (12.3% in BRV overall), and fatigue (9.5% in BRV overall).⁴⁹

CONCLUSION

Epilepsy is characterized as the chronic disorder of hypersynchronous neuronal electrical disturbances that recurrently occur. There are approximately 30 antiepileptic agents with FDA approval being used and they each offer therapeutic value that is accompanied by adverse effects. Brivaracetam is a 4-n-propyl derivative of levetiracetam that is used as adjuvant therapy for focal onset seizures. FDA-approved in 2016, the mechanism of action is not entirely understood; however, its anticonvulsant properties are believed to be related to its high affinity for the synaptic vesicle protein 2A found in the brain. The clinical trials that have been completed on brivaracetam show promising results while being well tolerated by the vast majority of the population who have taken the drug. Further studies are indicated to observe its long term efficacy and adverse effects.

ETHICAL CONSIDERATIONS

HCA Centralized Algorithms for Research Rules on IRB Exemptions (CARRIE)/ IRB manager issued study exemption # 2022-739.

CONFLICTS OF INTEREST

None of the authors report any conflicts of interest.

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Table 1. Brivaracetam Trials

Study type	Author (Year)	Groups Studied and Intervention	Results and Findings	Conclusions
Phase IIb, double-blind, randomized, parallel-group, placebo-controlled, dose-ranging study	French et al 2010 ⁴⁴	<p><u>Population:</u> 208 patients ranging in age from 16–65 years old with epilepsy experiencing ≥ 4 POS (refractory partial-onset seizures) during a 4-week baseline despite 1–2 concomitant antiepileptic drugs</p> <p><u>Intervention:</u> Randomized (1:1:1:1) to placebo BRV 5 mg/day BRV 20 mg/day BRV 50 mg/day administered BID during a 7-week treatment period</p>	<p>Reductions from baseline in POS frequency/week:</p> <ul style="list-style-type: none"> - 21.7% (placebo) - 29.9% (BRV5; $p = 0.086$) - 42.6% (BRV20; $p = 0.014$) - 53.1% (BRV50; $p < 0.001$) 	Statistical significance was observed in the BVR 50 group at the primary endpoint. This indicates that 50 mg of BVR is the ideal dosage for adults 16-65 with epilepsy experiencing 4 or more refractory partial onset seizures.
Phase IIb, double-blind, randomized, placebo-controlled, parallel-group, dose-ranging study	Paesschen et al 2013 ⁴⁵	<p><u>Population:</u> 157 patients ranging in age from 16-65 years old with 4 or more POS during a 4-week baseline despite treatment with 1-2 concomitant antiepileptic drugs were enrolled with intent-to-treat with 148 completing the study</p> <p><u>Intervention:</u> The groups were randomized into three groups that would be up-titrated to a placebo, 50 mg/daily, or 150 mg/daily group. The titration would be completed by week 3 and there was a 7-week maintenance phase for a total of 10 weeks.</p>	<p>At 7-week check: The median partial-onset seizure frequency/week: - 50 mg BVR 1.00 (0.71–2.38) - 150 mg BVR 1.96 (1.14–3.07) - Placebo 1.86 (0.94–4.69)</p> <p>At 10-week check: - 50 mg BVR 1.10 (0.70–2.00), - 150 mg BVR 2.05 (1.01–3.32) and - Placebo 1.95 (1.05–5.12)</p>	When checking for statistical significance after the 7-week maintenance phase, there was no statistical significance for the BVR 50 or BVR 150 groups when compared to the placebo but if the titration phase is considered and a comparison is made between BVR 50 and BVR 150 after 10 weeks of therapy, they are statistically significant.
Phase III, double-blind, randomized, placebo-controlled, fixed-dose-ranging study	Rylin et al 2014 ⁴⁶	<p><u>Population:</u> 398 patients ranging from 16-70 years old with focal epilepsy or epileptic syndrome with 2 or more focal seizures/month for 3 months prior to screening and eight or more focal seizures during an 8-week prospective baseline period who were also receiving 1 or 2 concomitant AEDs</p> <p><u>Intervention:</u> Randomized to BRV 20, 50, 100 mg/day, or</p>	<p>Median percent reductions from baseline were:</p> <ul style="list-style-type: none"> - 30.0% for BRV 20 mg/day ($p = 0.019$) - 26.8% for BRV 50 mg/day ($p = 0.092$) - 32.5% for BRV 100 mg/day ($p = 0.004$) - 17.0% for placebo 	Statistical significance was only observed in the BRV 100 mg/day group at the 12-week endpoint.

Study type	Author (Year)	Groups Studied and Intervention	Results and Findings	Conclusions
		placebo for 12 weeks		
Phase III, prospective, multicenter, randomized, double-blind, placebo-controlled, parallel-group, fixed-dose trial	Biton et al 2014 ⁴⁷	<p><u>Population:</u> 396 patients ranging from 16-70 years old with well-characterized partial epilepsy not fully controlled despite treatment with one or two antiepileptic drugs were enrolled during an 8-week baseline period with a 12-week treatment period</p> <p><u>Intervention:</u> Patients received either a twice-daily placebo (PBO) or BRV (5, 20, or 50 mg/day)</p>	<p>Median percent reduction from baseline in partial-onset seizure frequency/ week:</p> <p>17.8% for placebo 20.0% for BRV 5 mg/day 22.5% for BRV 20 mg/day 30.5% for BRV 50 mg/day</p>	The reduction was statistically significant in the 50 mg/day BRV group (p = 0.003) while statistical significance was not found for BRV 5mg/day and BRV 20 mg/day. This may note the importance of higher dosing (until a limit is reached).
Phase III, randomized, double-blind, PBO-controlled, multicenter, parallel-group study	Klein et al 2015 ⁴⁹	<p><u>Population:</u> A total of 768 patients were enrolled with 696 completing the study, patients ranged in age from 16-80 years, with well-characterized focal epilepsy or epileptic syndrome, uncontrolled with one or two concomitant AEDs at stable dosage for at least 1 month before visit 1 (3 months for phenobarbital, phenytoin, and primidone).</p> <p><u>Intervention:</u> Patients were given a placebo, 100 mg/daily BVR or 200 mg/daily BVR with an 8-week prospective baseline period, 12-week treatment period, and a 4-week down-titration period followed by a 2-week drug-free period, or entry into a long-term follow-up study.</p>	<p>Percent reduction over placebo in 28-day adjusted seizure frequency:</p> <p>22.8% for BRV 100 mg/day (13.3-31.2%; p < 0.001) 23.2% for BRV 200 mg/day (13.8-31.6%; p < 0.001)</p>	The reduction over placebo for seizure frequency was statistically significant in both the BRV 100 and BRV 200 group. Interestingly, response to BRV 100 mg/day was seen across all regions, however, for BRV 200 mg/day, there appeared to be a higher response in North America, Latin America, Asia-Pacific/Other countries, and non-EU European countries than in EU countries. This may indicate a genetic component to the drug's response and metabolism.

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